Alcohol consumption and risk of non-Hodgkin lymphoma: a pooled analysis

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Summary

Background **Previous epidemiological studies of the relation between alcohol consumption and risk of non-Hodgkin lymphoma (NHL) have been inconsistent, probably because of small sample sizes of individual studies that result from stratification by NHL subtype and type of alcoholic beverage. We aimed to assess the role of alcohol consumption in NHL with sufficient sample size to analyse by both type of alcoholic beverage and disease subtype.**

Methods **We obtained original data from nine case-control studies from the USA, UK, Sweden, and Italy in the International Lymphoma Epidemiology Consortium (InterLymph), yielding a pooled study population of 15 175 individuals (6492 cases and 8683 controls). We derived odds ratios (OR) and 95% CI from unconditional logistic regression models, controlling for study centre and other confounding factors. Heterogeneity between studies was assessed by comparison of results from joint fixed-effects logistic regression and two-stage random-effects logistic regression, and by calculation of Wald χ^2 statistics.**

Findings **People who drank alcohol had a lower risk of NHL than did non-drinkers (OR 0·83 [95% CI 0·76–0·89]). Compared with non-drinkers, risk estimates were lower for current drinkers than for former drinkers (0·73 [0·64–0·84] *vs* 0·95 [0·80–1·14]), but risk did not decrease with increasing alcohol consumption. The protective effect of alcohol did not vary by beverage type, but did change with NHL subtype. The lowest risk estimates were recorded for Burkitt's lymphoma (0·51 [0·33–0·77]).**

Interpretation **People who drink alcoholic beverages might have a lower risk of NHL than those who do not, and this risk might vary by NHL subtype. Further study designs are needed to determine whether confounding lifestyle factors or immunomodulatory effects of alcohol explain this association.**

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Introduction

Non-Hodgkin lymphoma (NHL) is a group of heterogeneous diseases characterised by the malignant transformation of healthy lymphoid cells.[1] Incidence of NHL has risen worldwide in past decades,[2,3] and in developed countries, NHL is the sixth most common cancer in men and eighth most common in women.[4]

Several epidemiological studies have associated alcohol consumption with NHL, although results have been inconsistent. Six population-based case-control studies[5–10] and a cohort study[11] have suggested that alcohol consumption reduces the risk of NHL, whereas four population-based[12–15] and five hospital-based[16–22] case-control studies found no association between alcohol consumption and NHL. Furthermore, positive associations between alcohol consumption and NHL have been reported in men[12] and in men with a family history of haemolymphoproliferative cancer[5] in two population-based case-control studies, and in cigarette smokers in a cohort study.[23] Epidemiological studies that have assessed alcohol consumption and NHL by type of alcoholic beverage[5–12,14,16,17,20,21,23,24] or by subtype of NHL[5–7,9,11,12,14,15,24] have reported conflicting results. If the association between NHL and alcohol consumption varies by disease subtype or by beverage type, individual epidemiological studies might have limited statistical power to analyse the relation.

The International Lymphoma Epidemiology Consortium (InterLymph) is a voluntary case-control consortium established in 2000 to facilitate collaboration among major epidemiological studies of lymphoma worldwide.[25] We aimed to assess the role of alcohol consumption in NHL with sufficient sample size to analyse by type of alcoholic beverage and by disease subtype.

Methods

Study population

We did a pooled analysis of original data from nine case-control studies identified through InterLymph. Studies were eligible if they had been completed between Jan 1, 1990, and Jan 1, 2004; had available electronic data at May 1, 2004; and had data for alcohol consumption. Data were pooled from nine case-control studies six of which had been reported previously.[8–10,12,14,20,21]

Data gathering and exposure definitions

Data for the nine participating studies were obtained mainly by use of interviews with standardised, structured questionnaires. In six studies,[8–10,14,20,21,26,27]

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trained interviewers asked questions about lifetime alcohol consumption in person. In the National Cancer Institute-Surveillance, Epidemiology, and End Results (NCI-SEER),[28] Nebraska,[29] and Sweden[12] studies, a food-frequency questionnaire that asked about usual alcohol consumption as an adult was mailed to individuals. Data for demographics and potentially confounding exposures, including body-mass index, history of NHL in a first-degree relative, and cigarette smoking were obtained during interviews done in person in all studies except Nebraska[29] and Sweden,[12] which gathered these data during a telephone interview.

The protocol for this pooled analysis was approved by the human-investigations committee at Yale University, New Haven, CT, USA. Informed consent was obtained in individual studies, which were approved by local human-investigations committees. From every study, we requested original questionnaires; descriptions of study methods; and a dataset that excluded personal identifiers and included variables on alcohol consumption, case or control status, NHL subtype for cases, sex, age, ethnic origin, body-mass index, history of NHL in a first-degree relative, cigarette smoking, and socioeconomic status. Participants who were known to be HIV positive were excluded from analyses. Original data from every study were obtained electronically and coded uniformly. Datasets were checked for internal consistency and agreement with results published previously; discrepancies were resolved with the study investigators.

We created a uniform set of exposure variables for alcohol consumption by comparison of study questionnaires. Non-drinkers were defined as those who consumed alcohol less than once a month as an adult and ever drinkers as those who consumed alcohol more than once per month as an adult. Current or former drinking status was defined at least 2 years before the date of diagnosis in cases or interview in controls. Data for beer, wine, and liquor consumption were collected and analysed separately, and then summed to estimate total alcohol consumption. The frequency of alcohol consumption was estimated with a standardised portion: a 355-mL bottle or can of beer, a 118-mL glass of wine, and a 44-mL shot of liquor. Intensity of ethanol consumption (g per week) was calculated by number of servings×ethanol per serving (beer 12·9 g, wine 9·3 g, and liquor 15·9 g). Lifetime consumption of alcohol (in kg) was calculated by use of data for intensity and duration of consumption (ie, kg of ethanol consumed per year×duration of consumption). Beverage preference (ie, beer, wine, or liquor) was assigned to study participants whose consumption of one type of alcohol consisted of 75% or more of their alcohol consumption in g per week. Continuous exposure variables for alcohol consumption were categorised into quartiles on the basis of the distribution in controls who drank alcohol; age and body-mass index were categorised into quartiles on the basis of distribution in all controls.

Sex, age, ethnic origin, body-mass index, family history of NHL, cigarette smoking, and socioeconomic status were potential confounding factors or effect modifiers in this pooled analysis. In the studies done in the USA, Italy, and Sweden, socioeconomic status was estimated by use of the highest level of education attained and grouped into tertiles. Because the distribution of education levels differed between these countries, the tertiles were defined separately on the basis of the distributions of controls in every study. In the UK, socioeconomic status was estimated by the original investigator by use of a continuous deprivation indicator derived for all small census areas in the UK and linked to the respondents' addresses.

Classification of NHL subtypes

In every study, cases were classified into NHL subtypes by pathologists who reviewed pathology samples and pathology reports. Five studies (Connecticut,[9] Sweden,[12] UK,[14] NCI-SEER,[28] and Nebraska[29]) classified NHL subtypes by use of the WHO NHL classification system.[1] The University of California at San Francisco (UCSF),[8] University of Southern California (USC),[10] northern Italy,[20,21] and Italy[26,27] studies classified NHL subtypes by use of the Working Formulation[30] because the WHO system had not been developed at the time of case recruitment. 118 cases were not classified by NHL subtype in the Milan study centre in the northern Italy study. Classification systems from every study were combined on the basis of codes from the International Classification of Diseases for Oncology,[31,32] previous research on NHL subtypes and classifications,[1,2,30,33–35] and consultation with a pathologist (FD) who was skilled in the diagnosis of lymphomas. We analysed risk of six B-cell NHL subtypes (Burkitt's lymphoma; chronic lymphocytic leukaemia or small lymphocytic lymphoma; and diffuse, follicular, mantle-cell, and marginal zone lymphoma) and three T-cell subtypes (mycosis fungoides or Sézary syndrome, peripheral, and other) as defined by the WHO NHL classification system.[1,32] 1090 cases who could not be classified into these groups were defined as other and were excluded from subtype-specific analyses.

Statistical analysis

Odds ratios (OR) and 95% CI were derived from dichotomous and polytomous unconditional logistic-regression models as estimates for risk of NHL and NHL subtypes, respectively. Fixed-effects estimates for the pooled data were derived from models controlled for study centre using the 24 centres or geographic regions for the nine studies (table 1). Sex, age (⩽45 *vs* 46–55 *vs* 56–65 *vs* ⩾66 years), and ethnic origin (white *vs* black *vs* other) were included in all models because these variables were used as matching criteria in several of the original studies. Socioeconomic status (low *vs* medium *vs* high) was included in all models because it

	Location	Year	Cases (n=6492)				Controls (n=8683)			
			Age (years)	n	Participation (%)*	Matching criteria	Source	n	Participation (%)*	Ref
University of California at San Francisco (UCSF)	San Francisco, CA, USA	1988–95	21–74	1304	72	Frequency matched by age, sex, and county of residence	RDD	2402	78	8
Connecticut	CT, USA	1995–2001	21–84	601	72	Frequency matched by age	<65 years: RDD ≥65 years: random selection from CMMS files	718	RDD: 69 CMMS: 47	9
University of Southern California (USC)	Los Angeles, CA, USA	1989–92	18–75	375	68	Individually matched by age, sex, ethnic origin, language of interview, and residential neighbourhood	Neighbourhood address	378	66	10
Sweden	Areas throughout	2000–02	18–74	613	76	Frequency matched by age and sex	Random selection from Swedish population register	480	69	12
UK	Parts of north and southwest England	1998–2001	18–64	686	75	Individually matched by age, sex, and region (north or south)	Random selection from general-practice lists	899	71	14
Northern Italy†	Aviano; Milan	1983–92	17–79	429	>97	None	Patients admitted to hospital for acute, non-neoplastic, non-immunological conditions in hospitals where cases were diagnosed	1157	>97	20,21
Italy‡	Turin; Novara; Vercelli; Varese; Verona; Forlì; Florence; Siena; Latina; Ragusa; Imperia	1990–93	20–74	1653	82	Frequency matched by age, sex, and area of residence	Random selection from demographic or national health service files	1771	74	26,27
National Cancer - Institute-Surveillance, Epidemiology, and End Results multicentre study (NCI-SEER)‡	Detroit, MI, USA; IA, USA; Los Angeles, CA, USA; Seattle, WA, USA	1998–2001	20–74	487	76	Frequency matched by age, sex, and study site	<65 years: RDD ≥65 years: random selection from CMMS files	414	52	28
Nebraska‡	NE, USA	1999–2002	20–75	344	74	Frequency matched by age and sex	RDD	464	78	29

RDD=random digit dialing. CMMS=Centers for Medicare and Medicaid Services. *Number participated/number eligible. †Hospital-based case-control study; all other studies were population-based (ie, cases were identified from hospitals and registries). ‡Findings of relation between alcohol and NHL have not been reported previously: ref provides additional information on study methods.

Table 1: **Characteristics of case-control studies included in pooled analysis**

accounted for a change of more than 10% in at least some risk estimates. Body-mass index (<22·5 *vs* 22·5–24·9 *vs* 25·0–27·4 *vs* ≥27·5 kg/m^2), family history of NHL (past history *vs* no history), and history of cigarette smoking (ever *vs* never in pack-years) were excluded from the final model because they did not change the risk estimate by more than 10%. Individuals with missing data for any variable were excluded from that analysis. Data were missing for less than 1% of all covariates, except for body-mass index (data not available for USC and Italy studies, 28% of pooled study population) and family history of NHL (data not available for northern Italy and Sweden studies, 18% of pooled study population). For studies with data for all covariates, inclusion of body-mass index and family history of NHL did not substantially change the risk estimates.

Heterogeneity in risk estimates between study centres was assessed by use of a Wald χ^2 test with inclusion of an interaction term in the dichotomous and polytomous logistic-regression models under the null hypothesis of no difference in risk estimates between studies. A two-stage method for analysis of pooled data was used to compare risk estimates from fixed-effects models with those from random-effects models to assess the effect of heterogeneity between studies on risk estimates.[36] First, we calculated NHL risk estimates with unconditional logistic-regression models for every study. Second, random-effects risk estimates (ie, OR and 95% CI) were derived with a weighted mean of individual study estimates, weighting the natural logarithm of every study OR by

	Non-drinker (controls/cases)	Ever drinker (controls/cases)	OR (95% CI)*
Connecticut	233/230	485/371	0·82 (0·65–1·04)
NCI-SEER	165/244	249/243	0·59 (0·44–0·78)†
Nebraska	213/174	251/170	0·81 (0·60–1·09)
UCSF	549/401	1853/903	0·77 (0·65–0·90)
USC	160/191	218/184	0·73 (0·54–0·99)
Northern Italy	177/67	980/362	0·82 (0·59–1·15)†
UK	123/95	776/591	0·99 (0·73–1·33)†
Italy	385/362	1386/1291	0·90 (0·75–1·07)†
Sweden	32/40	448/573	1·12 (0·68–1·85)
Pooled data	2037/1804	6646/4688	0·83 (0·76–0·89)‡

*Adjusted for age, sex, ethnic origin, and socioeconomic status.
†Adjusted for study centre or geographic region.
‡Joint fixed effects model; also adjusted for study centre.

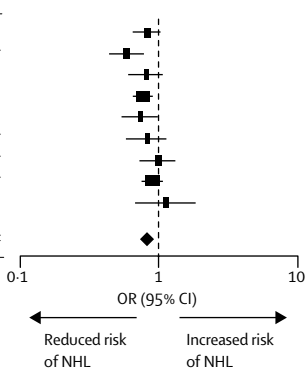

Figure: **Risk of NHL with alcohol consumption**

	Controls (n=8683)	Cases (n=6492)	OR (95% CI)*	p†
All studies				
Non-drinker	2037	1804	1·00	
Ever drinker	6646	4688	0·83 (0·76–0·89)	
Beverage type‡				
Beer only	1477	1061	0·85 (0·76–0·95)	
Wine only	624	459	0·85 (0·74–0·99)	
Liquor only	277	218	0·90 (0·74–1·09)	
Wine and beer	967	692	0·85 (0·75–0·96)	
Wine and liquor	946	618	0·79 (0·70–0·90)	
Beer and liquor	488	361	0·86 (0·73–1·01)	
Beer, wine, and liquor	1866	1272	0·76 (0·68–0·84)	
Frequency (servings per week)‡				
1–6	2786	2027	0·81 (0·74–0·88)	0·97
7–13	1365	958	0·83 (0·74–0·92)	
14–27	1345	951	0·85 (0·76–0·95)	
⩾28	1149	745	0·87 (0·76–0·99)	
Connecticut, UCSF, Italy (Verona), and Sweden studies				
Non-drinker	843	709	1·00	
Ever drinker	2935	1988	0·79 (0·70–0·90)	
Current‡	2392	1601	0·73 (0·64–0·84)	
Former‡	534	375	0·95 (0·80–1·14)	
Years since quitting‡				
1–5	253	150	0·89 (0·70–1·14)	0·90
6–14	162	115	0·97 (0·74–1·26)	
⩾15	116	102	1·01 (0·75–1·35)	
Connecticut, UCSF, and Italy (all centres) studies				
Non-drinker	1167	993	1·00	
Ever drinker	3724	2565	0·83 (0·75–0·92)	
Age at start of consumption‡				
<20	1491	947	0·80 (0·71–0·92)	0·30
20–29	1605	1073	0·80 (0·71–0·90)	
⩾30	582	482	0·91 (0·79–1·06)	
Connecticut, UCSF, northern Italy, and Italy (Verona) studies				
Non-drinker	988	736	1·00	
Ever drinker	3467	1777	0·78 (0·69–0·88)	
Duration (years)‡				
1–20	977	389	0·74 (0·63–0·88)	0·38
21–30	815	386	0·81 (0·68–0·95)	
31–40	739	417	0·76 (0·65–0·90)	
⩾41	925	571	0·81 (0·69–0·95)	
Lifetime consumption (kg)‡				
1–100	1218	639	0·78 (0·68–0·90)	0·83
101–200	597	293	0·80 (0·67–0·95)	
201–400	637	289	0·74 (0·62–0·89)	
⩾401	1010	553	0·80 (0·68–0·95)	

*Adjusted for study centre, age, sex, ethnic origin, and socioeconomic status. †p for linear trend. ‡ Data available only for completed questionnaires.

Table 2: **Risk of NHL associated with alcohol consumption**

the inverse of the sum of the variance of individual study estimates plus an estimate of the random-effects variance. Random-effects variance was calculated with moment estimation, which gives an unbiased, non-iterative estimator. Because the pooled OR and 95% CI obtained by use of joint fixed-effects and two-stage random-effects logistic-regression models were consistent for all analyses, we present results only from unconditional joint fixed-effects logistic-regression models.

We used Wald χ^2 tests to assess whether the effect of alcohol consumption on NHL risk varied by type of alcohol or by NHL subtype. The effect of age, sex, family history of NHL, and history of cigarette smoking on risk was assessed by use of the multiplicative model. These variables were chosen on the basis of findings from previous epidemiological studies.[5,11,14,17,23] Analyses of the linear trend for frequency of alcohol consumption (servings per week) and of the duration of alcohol consumption (years) were done for drinkers only by including variables for alcohol exposure as continuous variables in logistic-regression models; non-drinkers were excluded from these models to assess a potential dose-response relation in drinkers only. Statistical tests were two-sided with an α level of 0·05. Statistical analyses were done with SAS software version 8.2.

Role of the funding source

The sponsor of the pooled analysis and the funding sources for the case-control studies had no role in study design; collection, analysis, or interpretation of data; or writing of the report. The corresponding author had full access to the pooled data and had final responsibility for the decision to submit for publication.

Results

Table 1 shows selected characteristics for every study. The pooled study population of 8683 controls and 6492 cases consisted of 7864 men and 7311 women, 95% of whom were of white ethnic origin. The median age was 58 years (range 17–86). 2605 (30%) controls were in the highest category for socioeconomic status compared with 1690 (26%) cases (p<0·0001). By contrast, more cases than controls had a body-mass index of 27·5 kg/m^2 or more (1206 of 4433 [27%] *vs* 1418 of 6505 [22%]; p<0·0001), history of cigarette smoking (3695 of 6467 [57%] *vs* 4851 of 8646 [56%]; p=0·2066), and family history of NHL in a first-degree relative (164 of 5402 [3%] *vs* 121 of 7010 [2%]; p<0·0001). Among controls, alcohol drinkers were more likely to be young white men with a low body-mass index who smoked and who were more highly educated compared with non-drinkers (data not shown). However, the distribution of these variables between drinkers and non-drinkers differed by type of alcohol consumed (data not shown).

In the pooled data, drinkers had a significantly lower risk of NHL than did non-drinkers (figure). Risk of NHL associated with alcohol consumption did not differ between study centres (χ^2 27·3 [df 23], p=0·2443). We found no consistent dose-response relation between risk of NHL and age at start of alcohol consumption, frequency and duration of alcohol consumption, and total lifetime consumption of alcohol (table 2). However, data for Connecticut, UCSF, Italy (Verona), and Sweden showed that compared with non-drinkers, the risk for current drinkers was lower than that for former drinkers (table 2).

	Burkitt's (n=111)		CLL/SLL (n=991)		Diffuse (n=2126)		Follicular (n=1307)		Mantle-cell (n=196)		Marginal zone (n=231)		MF (n=98)		Peripheral T-cell (n=76)		Other T-cell NHL (n=148)	
	OR (95% CI)*	p†	OR (95% CI)*	p†	OR (95% CI)*	p†	OR (95% CI)*	p†	OR (95% CI)*	p†	OR (95% CI)*	p†	OR (95% CI)*	p†	OR (95% CI)*	p†	OR (95% CI)*	p†
Alcohol exposure																		
Non-drinker	1·00		1·00		1·00		1·00		1·00		1·00		1·00		1·00		1·00	
Ever drinker	0·51 (0·33–0·77)		0·94 (0·79–1·13)		0·75 (0·66–0·84)		0·84 (0·73–0·97)		1·03 (0·70–1·53)		1·02 (0·73–1·42)		0·69 (0·44–1·09)		0·96 (0·54–1·71)		0·66 (0·45–0·98)	
Current‡	0·29 (0·13–0·64)		0·89 (0·67–1·19)		0·64 (0·53–0·77)		0·83 (0·66–1·03)		0·55 (0·26–1·18)		0·89 (0·46–1·73)		0·70 (0·38–1·27)		0·40 (0·11–1·49)		0·62 (0·30–1·28)	
Former‡	0·47 (0·16–1·35)		1·08 (0·72–1·63)		0·92 (0·72–1·17)		0·97 (0·72–1·30)		2·04 (0·62–6·72)		1·76 (0·75–4·15)		0·72 (0·30–1·71)		1·19 (0·28–4·96)		0·48 (0·13–1·81)	
Frequency (servings per week)																		
1–6	0·60 (0·37–0·96)	0·11	0·80 (0·65–0·99)	0·13	0·76 (0·67–0·87)	0·53	0·82 (0·70–0·96)	0·83	0·88 (0·56–1·37)	0·62	1·10 (0·78–1·55)	0·30	0·68 (0·40–1·14)	0·02	1·07 (0·58–1·98)	0·12	0·73 (0·47–1·14)	0·72
7–13	0·42 (0·21–0·85)		0·93 (0·73–1·19)		0·73 (0·62–0·85)		0·80 (0·65–0·98)		1·39 (0·85–2·27)		0·95 (0·59–1·53)		0·91 (0·50–1·66)		0·92 (0·42–2·02)		0·64 (0·36–1·15)	
14–27	0·41 (0·19–0·92)		1·16 (0·91–1·46)		0·73 (0·61–0·86)		0·97 (0·78–1·20)		0·92 (0·54–1·57)		0·70 (0·40–1·23)		0·65 (0·32–1·33)		0·70 (0·29–1·69)		0·59 (0·33–1·04)	
⩾28	0·36 (0·14–0·89)		1·16 (0·88–1·52)		0·73 (0·60–0·90)		0·82 (0·63–1·07)		1·38 (0·78–2·42)		0·97 (0·52–1·84)		0·38 (0·14–1·03)		0·71 (0·26–1·98)		0·59 (0·31–1·09)	
Duration (years)§																		
1–20	0·50 (0·21–1·15)	0·16	0·78 (0·49–1·24)	0·86	0·72 (0·56–0·92)	0·18	0·74 (0·54–1·00)	0·82	0·60 (0·15–2·46)	0·80	0·76 (0·25–2·33)	0·79	0·53 (0·22–1·28)	0·62	NA		0·82 (0·36–1·87)	0·19
21–30	0·24 (0·08–0·76)		1·16 (0·77–1·74)		0·74 (0·57–0·94)		0·95 (0·72–1·27)		0·84 (0·21–3·40)		1·26 (0·41–3·92)		0·56 (0·23–1·35)				0·57 (0·21–1·51)	
31–40	0·27 (0·07–0·99)		1·03 (0·70–1·52)		0·72 (0·57–0·93)		0·82 (0·61–1·09)		0·48 (0·14–1·73)		1·07 (0·38–3·05)		0·65 (0·27–1·55)				0·58 (0·19–1·78)	
⩾41	0·34 (0·11–1·04)		0·81 (0·58–1·15)		0·67 (0·53–0·85)		0·84 (0·63–1·12)		0·51 (0·19–1·36)		0·62 (0·26–1·48)		1·08 (0·50–2·32)				0·76 (0·27–2·15)	

CLL/SLL=Chronic lymphocytic leukaemia/small lymphocytic lymphoma. MF=Mycosis fungoides/Sézary syndrome. NA=Insufficient sample size to estimate risk. *OR for comparison with non-drinkers adjusted for study centre, age, sex, ethnic origin, and socioeconomic status. †p for linear trend. ‡Data for CT, USCF, Italy (Verona), and Sweden studies only. §Data for CT, USCF, northern Italy, and Italy (Verona) studies only.

Table 3: **Risk of NHL subtypes associated with alcohol consumption**

The association between alcohol consumption and lowered risk of NHL did not vary by beverage type, and risk did not differ by the combination of beverages consumed (7·9 [6], p=0·2439; table 2). In the NCI-SEER and Nebraska studies, those who drank wine only were at a lowered risk of NHL compared with non-drinkers (OR 0·88 [95% CI 0·78–0·99]) that did not vary by type of wine (red 0·74 [0·45–1·22]; white 0·85 [0·51–1·40]). Age, sex, family history of NHL, or history of cigarette smoking did not modify the effect of alcohol consumption on risk of NHL or NHL subtypes with the multiplicative model (data not shown).

The effect of alcohol on risk of NHL varied with B-cell NHL subtype (χ^2 14·0 [df 5], p=0·0155; table 3), with the lowest risk noted for Burkitt's lymphoma. Compared with non-drinkers, ever drinkers had about half the risk of developing Burkitt's lymphoma, in whom the lowest risk was recorded for current drinkers. The type of beverage did not affect the association between alcohol consumption and Burkitt's lymphoma (4·2 [6], p=0·6511). Table 3 shows the association between increasing frequency and duration of alcohol consumption and risk of Burkitt's lymphoma, which was approximately linear for frequency of consumption only and was not significant. When analyses included 49 people with Burkitt's lymphoma from studies in which more than 70% of the population participated, risk for ever drinkers (OR 0·36 [95% CI 0·19–0·66]) remained significant. Among these ever drinkers, current drinkers were at lower risk than were former drinkers (0·29 [0·12–0·69] *vs* 0·40 [0·13–1·30]). Furthermore, in studies in which more than 70% of the population participated, people who drank alcohol had a lower risk of developing any type of NHL than did non-drinkers (0·85 [0·77–0·94]).

Alcohol consumption was associated with a lowered risk of diffuse and follicular lymphomas. However, no clear dose-response relation was seen for either diffuse or follicular NHL subtypes (table 3). Ever consumption of alcohol was associated with lowered risk of other T-cell NHL (ie, non-peripheral T-cell lymphoma and non-mycosis fungoides/Sézary syndrome), but overall the effect of alcohol consumption did not differ between T-cell NHL subtypes (χ^2 1·1 [df 2], p=0·5656).

Discussion

Our pooled analysis of 15 175 study participants from nine case-control studies suggests that people who drink alcoholic beverages have a lower risk of NHL than those who do not. In participants from the Connecticut, UCSF, Italy (Verona), and Sweden studies, current drinkers were 0·73 times as likely as non-drinkers to develop NHL. We found no dose-response relation for increasing frequency and duration of consumption, or total lifetime consumption. The type of alcoholic beverage consumed did not affect risk. However, risk varied by NHL subtype, with the lowest risk recorded for Burkitt's lymphoma.

Alcohol increases the risk of several cancers, including those of the oral cavity, oesophagus, and liver. However, the mechanism of carcinogenesis is not clear, and the potential protective effects of alcohol are even less well understood.[37] The potential protective effects of alcohol could be due to its immunomodulatory effects, which have been investigated mainly in people who consume very high amounts of alcohol, including alcoholics. Although heavy alcohol consumption impairs immune function, light to moderate alcohol use (ie, up to one drink a day for women and two drinks a day for men) might improve cellular and humoral immune responses; however, this mechanism is not well described.[38] Furthermore, light to moderate consumption of alcohol has been associated with increased insulin sensitivity,[39–41] whereas heavy alcohol use might impair insulin sensitivity.[42] Because diabetes has been associated with increased risk of NHL,[43] alcohol might reduce the risk of NHL indirectly by increasing insulin sensitivity in otherwise healthy individuals.

Our findings are consistent with results from several epidemiological studies that were not included in this pooled analysis that reported reduced risk of NHL with alcohol consumption,[5–7,11,15] and with deaths from haematological cancers[44] in alcohol drinkers compared with non-drinkers, although the recorded protective effects of alcohol were not significant in all studies. To assess potential differences between case-control studies included in our pooled analysis and other published studies, we computed the logit estimate of the adjusted common OR from eight case-control studies that were not included in this pooled analysis[5–7,13,15,17–19,22] and presented an OR for the association between alcohol and NHL. The estimated adjusted common OR suggested a significant, but slightly weaker, association between alcohol consumption and reduced risk of NHL (OR 0·92 [95% CI 0·89–0·96]), which was consistent with our results. In studies[5–7,9,11,12,14,15,24] that have assessed the relation between alcohol consumption and NHL by disease subtype, alcohol has been weakly associated with a decreased risk of the major NHL subtypes (eg, diffuse and follicular lymphomas and chronic lymphocytic leukaemia or small lymphocytic lymphoma); data for other subtypes have generally not been reported.[5–7,9,11,14] In a PubMed search for articles published in English (1980–2004), we did not find any published reports of the association between alcohol consumption and risk of Burkitt's lymphoma.

Although we found that people who drank alcohol had a lower risk of NHL than did non-drinkers, we found no dose-response relation for frequency or duration of consumption. Our definition of usual adult consumption might not have accurately recorded current or recent consumption, weakening the effect. Moreover, the absence of a dose-response relation for duration of consumption might be expected if only current or recent exposure changes risk, as these data suggest, or might indicate a spurious relation by an unknown NHL risk factor. Moderate alcohol consumption is more common in individuals with high socioeconomic status,[45,46] and this variable was inversely related to NHL risk in our study. Adjustment of data for socioeconomic status changed risk only slightly, although education might be an inadequate measure of socioeconomic status. Adjustment for socioeconomic status and for red-meat, fruit, and total energy intake in the Iowa Women's Health Study[11] did not explain the effect of alcohol in those data. Our data suggest that European studies have higher proportions of drinkers and higher levels of alcohol consumption than do US studies, yet the protective effect of NHL is slightly greater in the US studies, possibly because of unmeasured confounding (eg, diet, reasons associated with abstention from alcohol, or an unknown factor), differences in drinking patterns, or differences between non-drinkers in the USA and Europe. However, the difference in risk for current and recent drinkers (ie, those who stopped drinking <5 years ago) compared with those who stopped drinking earlier (ie, >5 years ago), and the different effects of alcohol on NHL subtypes, might mitigate concerns about residual confounding, which would similarly affect all drinkers and all NHL subtypes.

In our study, risk was lower for Burkitt's lymphoma than for other NHL subtypes, but the reasons for this association are unclear. However, Epstein-Barr virus, a herpesvirus implicated in lymphomagenesis, is associated with 10–30% of Burkitt's lymphomas in developed countries, and is also associated with a smaller proportion of other types of NHL.[47] Because more than 90% of adults are carriers of Epstein-Barr virus, light to moderate consumption of alcohol might help maintain the immunological equilibrium between latent infection with this virus and carcinogenesis. Although the risk of the major NHL subtypes were much the same, we cannot rule out that our findings for Burkitt's lymphoma and other rare NHL subtypes are due to chance. However, the difference in current and former drinkers argues against this explanation for our subtype-specific findings.

The similarity of our results with joint fixed-effects and two-stage random-effects models suggests that interstudy heterogeneity is not an explanation for our findings. Comparable exposure measurement across studies and use of original data allowed us to define uniformly exposures—an advantage of doing a pooled analysis with original data rather than a meta-analysis on published data.[48] Although cases in this pooled analysis had histologically confirmed NHL, central review of all cases by a team of study pathologists was not feasible, and thus NHL classification rules might have differed between studies and some disease misclassification could have occurred for analyses by NHL subtype. Diagnostic accuracy with the WHO NHL classification system is estimated to be more than 80% for most NHL cases.[33,49] Disease misclassification was likely to be non-differential, thus biasing the results toward the null hypothesis. Furthermore, bias could have resulted from low participation in some studies if participation were differentially related to alcohol consumption in cases and controls. However, the magnitude of our results for overall NHL were consistent and remained significant when we restricted analyses to studies with participation rates of more than 70% (ie, Nebraska, UCSF, northern Italy, UK, Italy); the effects for Burkitt's lymphoma also persisted and remained significant, but with wider 95% CI. Moreover, 95% of the study population were white, and we thus could not assess the association between alcohol and NHL in people of other ethnic origin.

In our study, the association between alcohol consumption and risk of NHL could not be attributed to consumption of a specific type of alcoholic beverage. Laboratory studies have suggested that antioxidants in grape skins, such as resveratrol, reduce the risk of NHL in wine drinkers, especially those who drink red wine (due to the inclusion of grape skins in red-wine production).[38,50–54] However, our data do not lend support to a difference between the effects of red-wine and white-wine consumption. Several studies[5,11,14,17,23] have reported that the effect of alcohol on NHL risk varies by age, sex, family history of NHL, or history of cigarette smoking. In our study, alcohol consumption and risk of NHL was not significantly modified by any of these factors under the multiplicative model. Findings from previous studies might have arisen by chance on the basis of small sample sizes that result from population stratification.

In conclusion, our pooled analysis of alcohol consumption and NHL risk suggests that people who drink alcoholic beverages have a lower risk of NHL than those who do not. This relation does not seem to depend on the type of alcoholic beverage consumed, but might vary by NHL subtype. Future research to confirm these findings by use of prospective data, and to determine the likely biological mechanism, is warranted.

Contributors

L M Morton helped obtain funding, analysed the data, and drafted and revised the report. T Zheng and P Hartge helped obtain funding; contributed, analysed, and interpreted the data; and revised the report. T R Holford helped obtain funding and with statistical analyses. E A Holly and J R Cerhan helped obtain funding, and contributed, analysed, and interpreted the data. B C H Chiu, A Seniori Costantini, E Stagnaro, E V Willett, L Dal Maso, D Serraino, E T Chang, W Cozen, S Davis, R K Severson, and L Bernstein contributed data. S T Mayne did data analyses and interpretation. F R Dee classified NHL subtypes. All authors contributed to the final version of this report.

Conflict of interest

We declare no conflicts of interest.

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